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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/129,758	08/05/1998	RAINER WALDMANN	1099-00	5113
35811 7590 12/26/2008 IP GROUP OF DLA PIPER US LLP ONE LIBERTY PLACE 1650 MARKET ST, SUITE 4900 PHILADELPHIA, PA 19103				
EXAMINER				
BASU, NIRMAL SINGH				
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1646				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

09/129,758

Applicant(s)

WALDMANN ET AL.

Examiner

NIRMAL S. BASI

Art Unit

1646

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1, 11-13, 15, 17-23, 26, 27, 30 and 31 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 11-13, 15, 17-23, 26-27, 30-31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

1. Amendment filed 8/18/08 has been entered.
2. Claims 1, 11-13, 15, 17-23, 26-27 and 30-31 are pending in the application and are examined below as pertaining to the elected invention.

Claim Rejections - 35 USC § 101 and 35 USC § 112, 1st paragraph

The following is a quotation of 35 U.S.C. 101:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1, 11-13, 15, 17-23, 26-27, 30-31 are rejected under 35 U.S.C. 101 for reason of record in the previous Office Action, and those given below, because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Applicants arguments pertaining to the rejection of claims 1, 11-13, 15, 17-23, 26-27 under 35 U.S.C. 101 and 112, first paragraph are summarized below:

Applicants generally argue the role of ASIC channels and arguments are similar to those addressed previously that regarding the link between ASIC channels and ischemia, ASIC channels and pain perception, ASIC channels and neurodegeneration, and ASIC channels and pain perception. Applicants are generally arguing that ASIC channels are activated by extracellular acidification and associated with a number of activities (nociception, taste transduction, anxiety disorder, pathologies such as cerebral neuronal degeneration), and these activities can readily be used by those skilled in the art. Applicant's arguments, and the earlier declaration Peter McNaughton have been fully considered but they are not found persuasive. The general activity of ion transport, possessed by the family of channel proteins, cannot be used to support utility in instant case.

In light of the specification, the skilled artisan can conclude that the protein of instant invention is a cationic channel protein. However, no disclosure is provided within the instant specification on what specific function the claimed cationic channel protein possesses, nor are any disease states disclosed that are directly related to the claimed channel dysfunction. A detailed argument to Applicants' traversal is provided below.

The references supplied by applicants and discussed below clearly show that the role of ASIC protein channels was unknown **at the time of filing** of instant application.

For example, see Chen et al (Proc. Natl. Acad. Sci. USA, Vol. 95, pp10240-10245, August 1998), **page 10245, column 1, last paragraph, which states ASIC channels have a widespread distribution in the central nervous system but as yet have an unknown physiological role.**

Allen et al (J. of Physiology, Vol 543 (2), pages 521-529, 2002), page 521, column 2, **discloses that little is known about the modulation of ASIC channels in the central neurons, ASIC channels require a large and rapid fall of pH to be activated and it is unclear when this might happen in the CNS.**

Wemmie et al (The Journal of Neuroscience, Vol. 23, (13) pages 5496-5502, 2003) page 5502, column1 **discloses that additional studies will be necessary to delineate the multiple possible effects of ASIC on behavior.**

Baron et al (Journal of Physiology, Vol 539(2), pages 485-494, 2002) page 485 **discloses that ASIC are functionally diverse and the role of ASIC1a, ASICa, ASIC2b and ASIC4 in the central neurons remains to be established.** Therefore, based on the art and the specification, the role of the claimed channel and its association with a specific disease or dysfunction was unknown at the time of filing of instant application.

Although the family of ASIC proteins domains may share some common structural motifs, various members of the family may have different sites of action and different biological effects. No disease states are disclosed that are directly related to claimed channel dysfunction. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polypeptide/nucleic acid or methods of its use. The specification provides a laundry list of diseases that may be associated with claimed invention but does not provide any data or nexus between the claimed invention and stated use. The claimed invention belongs to a family of ion transporting proteins, which have different electrophysiological properties and divergent physiological functions that result from the transport of said ions. The gated channels are a complex family of ion channel proteins with varied properties and functions (discussed in previous office action). The observation that the claimed invention is an amiloride-sensitive degenerative sodium channel and the disclosure of amiloride sensitivity and certain biophysical properties does not provide support for either a specific and substantial asserted utility or a well-established utility. The specification discloses, pages 2 and 3, the family of structural relatives of ASIC channels (also designated as MDEG) have different electrophysiological properties and that no normal physiological function of said MDEG was known until the demonstration of its activation by protons (also see page 17, lines 13-16). Also disclosed, page 5, inactivation and kinetics and the ionic selectivity of the channel formed after co-expression of different MDEG are different than those if only one channel is expressed. Therefore, expression of the various MDEGs in different tissues may have divergent functional effects due the presence of other channel proteins. The specification, page 5, lines 8-9 states, when referring to claimed ion channel, this property is very similar to that of the proton-activated cationic channel which is implicated in the prolonged sensation of pain caused by acidosis. It is very probable that DRASIC and MDEG2 are part of this channel. The claimed ion channel is speculated to be similar to the family of proton-activated ion

channels, but there is no disclosure in the specification as to the relationship of claimed invention to ischemia, pain perception, neurodegeneration, and which known ASIC channel blockers can be used to limit postischemic neuronal death. For example, would activating the claimed channel increase neurodegeneration or decrease it? The specification provides no answers.

All members of the ASIC family do not have the same electrophysiological properties (ASIC2b, does not respond to low pH, ASIC4 is inactive by itself and hence is not thought to encode a proton-gated ion channel), and members have been proposed to function in a wide variety of disease states e.g. pain sensation, ischemia, epilepsy, neurodegenerative diseases, but their role in the brain is obscure, see Berdiev et al in previous Office Action, Ref U, page 15023, second column. The function of these channels in the glia remains a mystery; see Berdiev et al, page 15023. Further it has been shown that constitutive amiloride-sensitive currents are a specific feature of the more aggressive brain tumors (see Berdiev et al, page 15034, column 1). Further, amiloride sensitivity cannot be used to infer a specific or well-established utility. Berdiev discloses the difficulty of assigning a function based on amiloride sensitivity. Berdiev, states (page 15034, column 1, second paragraph), "amiloride-sensitive sodium channels cannot easily be classified based on simple biophysical parameters, such as single channel conductance and/or sensitivity to amiloride. This class of ion channel, both in the brain and in epithelial tissues, appear to have a variable composition, and hence tissue-specific differences in biophysical parameters may result from different channel compositions in different tissues". Further the specification provides no significance of the function of amiloride (a drug that blocks sodium/proton antiport and has been used clinically as a potassium sparing diuretic) as it correlates to its role in pain sensation.

The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the ion channel of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants claimed invention is incomplete. In light of the specification the skilled artisan can conclude that protein of instant invention is a cationic channel protein. However, no disclosure is provided within the instant specification on what specific function the claimed cationic channel protein possesses, nor are any disease states disclosed that are directly related to cation channel dysfunction. Ions are known to play a role of first or second messenger in numerous cellular signaling contexts, but it is not known what role claimed cationic channel plays in signaling and what would be the use of interfering with its function, apart from as targets for drug discovery. Further it is not clear from the specification if the channel protein disclosed by the amino acid sequence of SEQ ID NO: 4 encoded by SEQ ID NO: 3 has ion transport activity. There is no disclosure in the specification, which shows the protein of SEQ ID NO: 4 was assayed for activity.

The utilities asserted by Applicant are not specific or substantial. Since no specific function of claimed cation channel is known, and the ability to transport ions with no associated function is not considered a well established utility, the hypothesized functions are based entirely on conjecture from homologous polypeptides. The asserted utilities are not specific to instant polypeptide, but rather are based on family attributes. Neither the specification nor the art of record discloses any compounds that treat a specific disorder associated with dysfunction of the nucleic acid of SEQ ID NO: 1, 3 or 8 or its encoded protein (SEQ ID NO: 2, 4 or 8). Similarly, neither the specification nor the art of record discloses any instances where disorders can be affected by interfering with the activity of claimed cation channel. Thus the corresponding asserted utilities are essentially methods of using the claimed cation channel to identify or treat disease states associated with cation channel polypeptide dysfunction and as targets for drug discovery. Therefore, the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with the claimed cation channel, which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed cation channel, further experimentation is necessary to attribute a utility to the claimed cation channel. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are useful to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of useful as it appears in 35 U.S.C. 101, which requires that an invention must have either an immediately apparent or fully disclosed real world utility. The court held that:

The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . . [i]t is not a reward for the search, but compensation for its successful conclusion.

The DNA of the instant invention and the protein encoded thereby are compounds, which share some structural similarity to other ion channel proteins based on sequence similarity. The family of proteins related to instant invention may have diverse effects and bind a diverse number of ligands (e.g. syntax , see Berdiev et al). Although the family of ASIC proteins domains may share some common structural motifs, various members of the family may have different sites of action and different

biological effects. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides/polypeptides. Also, the specification does not predict whether the claimed polynucleotides/polypeptides would be over expressed or under expressed in a specific, diseased tissue compared to the healthy tissue control. The specification contains assertions that the claimed polynucleotides/polypeptides can be used the art for drug development. However, without a disclosure of a particular disease state in which the claimed polynucleotides/polypeptides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression/protein expression monitoring assay mean. For example, if a compound is tested on a microarray comprising the claimed polynucleotides and affects expression of the polynucleotides negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would exacerbate the disease if administered. The test results also would not have meaning in terms of what specific disease is relevant. Further, before the claimed invention can have utility in gene expression, significant, further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are over expressed or under expressed in the diseased tissue. The disease state itself has to be identified.

The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids/polypeptides. Even if the expression of Applicants individual polynucleotides/polypeptides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

If a molecule is to be used as a surrogate for a disease state (e.g. gene therapy), some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. over expression). In instant case Applicants implicate Alzheimer's disease. Is claimed DNA/protein over-expressed or under expressed in Alzheimer's disease? There is no data in the specification or prior art that provides support for the claimed ion channel dysfunction resulting in Alzheimer's disease. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics/treatment for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby to any disease or disorder and the lack of any correlation with any known disease or disorder, the use of ASIC gene, or its encoded polypeptide, in therapy, would only serve as the basis for further research. "Congress

intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

The ASCI family is functionally highly diverse. When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here. The specification has not disclosed a specific disease or disorder of any type wherein the claimed polynucleotides/polypeptides are expressed at altered amounts or forms relative to the required control healthy tissue. Significant further research would be required of the skilled artisan to identify such a disease or disorder. Therefore the asserted utility is not substantial. The polypeptide encoded by the polynucleotide belongs to a family in which the members have divergent functions based on which tissues the protein is expressed or administered to. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. Although the ASIC belongs to a family of proteins that transport ions, the family has divergent functional effects as consequence of that ion transport, and cannot be compared to the ligase family of proteins, which have a specific effect, ligate DNA.

4. Claims 1, 11-13, 15, 17-23, 26-27, 30-31 are rejected under 35 U.S.C. 1 12, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons, one skilled in the art clearly would not know how to use the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIRMAL S. BASI whose telephone number is (571)272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nirmal S. Basi/
Examiner, Art Unit 1646

/Michael Pak/
Primary Examiner, Art Unit 1646
